Health Canada Santé Canada

Guidance Document

Post-Notice of Compliance (NOC) Changes: Framework Document

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Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

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Administrative Changes

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Nature of and/or reason for change:
Clarification of when Level III changes should be filed and the documentation that should submitted.

Consequential changes to include new initiatives that have been implemented over the past several years such as: the Notice on how Health Canada initiated safety changes for human drugs under the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law) (2014) are managed; and the Plain Language Labelling (PLL) Requirements for Level I changes to include Mock-up Labels for prescription drugs and those administered or obtained through a health professional came into force on June 13, 2015 and for all non-prescription drugs on June 13, 2017.

Date: August 27, 2018

Nature of and/or reason for change:

Clarification of when to file Level III Quality changes annually.

Foreword

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

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1. Introduction

After a new drug as defined in section C.08.001 of the Food and Drug Regulations has been granted a Notice of Compliance (NOC), it is not uncommon for sponsors to make changes to the drug. A post-NOC change is any change that is made to a new drug that has received a NOC pursuant to section C.08.004 of the Food and Drug Regulations. Many of these changes may be made to improve the quality of the drug product or the efficiency of the manufacturing process, or they could be made for marketing considerations. Changes to the labelling of a drug product could include adding new indications, improving the management of risk for a product by adding warnings, limiting the target population or changing the dosage regime etc.

1.1 Policy objectives

This guidance document together with the associated documents (refer to Section 2.3) provides an updated interpretation of section C.08.003 of the Food and Drug Regulations by:

i. providing criteria to define what is meant by significantly different[1] as it relates to the matters specified in C.08.003 (2), and
ii. providing sponsors with recommendations on the data required to enable Health Canada to make an accurate determination of the impact of a change on the safety, efficacy and quality of the new drug.

1.2 Policy statements

Health Canada recognizes that:

i. any change to a drug may impact the safety, efficacy and quality of that drug, and
ii. any change to the information associated with the drug (e.g., labelling) may impact the safe and effective use of that drug.

To enable Health Canada to manage risks that may be associated with a change to a new drug:

i. any change to a drug that has received a NOC should be reported according to one of the four following categories: Level I (Supplements), Level II (Notifiable Changes), Level III (Annual Notifications) and Level IV (Record of Changes) based on the criteria and conditions indicated in the associated guidance documents, and
ii. data to support a Level I or Level II change, as recommended in the associated guidances, should be submitted to Health Canada for review prior to implementing the change. Data to support a Level III change should not be submitted, but should be available to Health Canada upon request. Data to support a Level IV change should be retained by the sponsor or manufacturer.

1.3 Scope and application

The Framework, Safety and Efficacy and Quality guidance documents apply to sponsors intending to make changes to new drugs that have received a NOC pursuant to section C.08.004 of the Food and Drug Regulations. These drugs may include pharmaceuticals, biologics, and radiopharmaceuticals for human use and pharmaceutical, radiopharmaceutical and certain biotechnological products for veterinary use[2], including those submissions for which a NOC has been recommended but issuance of the NOC has been placed on hold. In the absence of a guidance specific to Quality changes to drugs which were approved through a Drug Identification Application - Biologics (DIN-B drugs), the Quality guidance document applies to those products.

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1 Section C.08.003(1) of the Food and Drug Regulations states in part:
"Despite section C.08.002, no person shall sell a new drug in respect of which a notice of compliance has been issued to the manufacturer of that new drug, if any of the matters specified in subsection (2) are significantly different from the information or material contained in the new drug submission...."

2 The Veterinary Drugs Directorate (VDD) should be consulted to determine if the submission constitutes a veterinary biotechnological drug under the Food and Drugs Act.

This guidance document should be read in conjunction with the other Health Canada documents as well as the following associated Post-Notice of Compliance (NOC) changes documents:

- the Post-Notice of Compliance (NOC) Changes: Quality,
- the Post-Notice of Compliance (NOC) Changes: Safety and Efficacy, and
- the Notice: How Health Canada is managing safety updates when a serious health risk is identified under the Protecting Canadians from Unsafe Drugs Act (Vanessa's Law) (April 22, 2016)

Information regarding general submission requirements and target performance standards may be found in the Health Canada guidance documents: Guidance Document: Management of Drug Submissions for drugs intended for human use and the Guidance for Industry: Management of Regulatory Submissions for drugs intended for veterinary use.

It is recommended that the principles established in these guidance documents be applied to similar Quality changes that occur during the development of the drug and the recommended supporting data is included with the initial New Drug Submission (NDS) or Abbreviated New Drug Submission (ANDS).

The following guidances and policies have been superseded by the Post-NOC Changes guidance documents:

- New Drug: Sufficient Time policy (1991)
- Extension of Expiration Dates (1991)
- Changes to Marketed New Drug Products policy (1994)
- Stability Requirements for Changes to Marketed New Drugs (1994)
- Changes in Product-Specific Facility Information (revised in 2004)
- New Drug: Sufficient Time notice (2005)
- Draft Guidance for Industry: Changes in Product Colours or Markings (2005)

1.4 Background

The New Drug: Sufficient Time policy released in 1991 was developed to "expedite the review process and reduce the backlog of New Drug Submissions". This was accomplished by eliminating the requirement for sponsors to file specified changes made to a drug, provided that the drug had been marketed for a minimum of seven years in Canada. The policy was based on the amount of time a drug has been marketed and has since been recognized as not encompassing modern evidence-based risk management principles. Therefore, in January 2005, the Notice: New Drug - Sufficient Time was issued as an interim measure to allow for better management of the potential risks that may be associated with a change to a drug regardless of the time it has been on the market.

In April 1994, Health Canada released the policy entitled Changes to Marketed New Drug Products. The purpose of this policy was to provide an interpretation of the requirements of section C.08.003 of the Food and Drug Regulations, to introduce a tiered structure for changes to marketed drugs and to reduce the review workload by decreasing the number of Supplemental New Drug Submission (SNDS) filings. The changes were grouped into four categories (Level 1, 2, 3 and 4) based on the significance of the change and therefore the potential impact on safety and efficacy.

As a follow-up to this, in March 1997, Schedule 733 - Changes to Marketed New Drugs was proposed in Canada Gazette Part I. The intent of this regulatory proposal was to introduce into the Food and Drug Regulations a graduated system of regulatory requirements for changes to new drugs marketed in Canada. However, this proposal to amend the Regulations was withdrawn in October 1998. It was believed at the time that this type of guidance would better be conveyed to stakeholders in the form of policies and guidance documents, rather than embedded in the Regulations, in order to allow Health Canada a greater ability to adapt to a rapidly changing international regulatory environment.

A number of international developments have occurred since the Changes to Marketed New Drug Products policy was first introduced in 1994. This includes the trend amongst competent regulatory authorities to emphasize an integrated approach to review and inspection based on scientific risk management prin

As such, the Post-NOC Changes series of guidance documents have been written taking into consideration the concepts of risk management, the practices of other Regulatory Agencies (specifically those of the United States, the European Union and Australia) as well as guidances produced by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) or the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) and adopted by Health Canada.

As the Branch is undertaking efforts to modernize the Food and Drugs Act and the frameworks for the regulation of therapeutic products, a decision was made that until this modernization is completed, it would be most efficient to keep the existing terminology and process structure for the four Levels (i.e. Supplement, Notifiable Change, Annual Notification and Record of Change), but with substitution of the new criteria. Thus these levels, although redefined to reflect modern risk/harm management principles, will retain their current status with respect to the existing Regulations.

2. Guidance for implementation

2.1 Reporting categories

A brief description of the reporting categories is provided below. More details regarding criteria specific to safety and efficacy or quality-related changes, along with examples are provided in the associated guidance documents listed in section 2.3 below. If the submission has been inappropriately classified, the sponsor will be notified at the screening stage.

2.1.1 Level I - supplements

Level I or Supplements are changes to a new drug that are "significantly different" as it relates to the matters specified in C.08.003 (2) of the Food and Drug Regulations and have the potential to impact the safety, efficacy, quality and/or effective use of the drug. The changes included in this reporting category shall be filed, along with the recommended supporting data, to Health Canada as a Supplement to a New Drug Submission (SNDS) or Supplement to an Abbreviated New Drug Submission (SANDS). The change may not be implemented by the sponsor until a NOC has been issued.

2.1.2 Level II - notifiable changes

Note: All Level II - Notifiable Changes (Quality) referred to in this document are not applicable to Human Pharmaceuticals.

Level II or Notifiable Changes (NC) are changes to a new drug that have the potential to impact the safety, efficacy, quality and/or effective use of the drug but do not require the issuance of a NOC. The changes included in this reporting category should be filed, along with the recommended supporting data, to Health Canada as a Notifiable Change. All Level II changes should not be implemented by the sponsor until a No Objection Letter (NOL) has been issued.

Multiple Level II (Quality) changes for the same drug product may be filed in a single submission provided those changes are related and/or supported by the same information. If the changes are related, the sponsor should indicate the association between the proposed changes.

Multiple Level II (Safety and Efficacy) changes for the same drug product may be filed in a single submission provided those changes are within the same reporting category (i.e., multiple 90 day NCs in one submission or multiple 120 day NCs in one submission).

If there are too many changes filed within the same submission or major issues are identified with a change which would require extensive time to review, Health Canada may divide the changes into separate submissions.

For submissions that include multiple changes, the sponsor should clearly specify which supporting data supports which change.

If the same change is applicable to multiple drugs, a separate submission is required for each drug product but the data may be cross-referenced.

2.1.3 Level III - annual notifications

Level III or Annual Notifications are changes to a new drug that have minimal potential to impact the safety, efficacy, quality and/or effective use of the drug. The changes included in this reporting category may be implemented by the sponsor without the prior review by Health Canada of the data supporting such a change.

A Level III change should be submitted at the time the change is implemented, or submitted during the Annual Drug Notification period[3] depending on the type of drug (e.g., pharmaceutical or biologic) and the type of change (Quality or Safety and Efficacy). All Level III changes should be submitted using the Post-Notice of Compliance (NOC) Changes: Level III change form.

For biologics (Schedule D drugs) and radiopharmaceuticals (Schedule C drugs), notification of all Level-III Quality changes that have occurred in the preceding twelve (12) months should be provided annually during the Annual Drug Notification period using the Post-Notice of Compliance (NOC) Changes: Level III change form.

In some instances, after a Level III change has been implemented and Health Canada's awareness of the change is considered necessary, the sponsor may be requested to file an Immediate Notification. A sponsor may also wish to file an immediate Notification for the same reason stated above.

For pharmaceutical drugs for human or veterinary use, Health Canada recommends that Level III Quality changes be filed at the time the change is implemented.

For biologics, radiopharmaceuticals and pharmaceutical drugs for human or veterinary use, Health Canada recommends that Level III Safety & Efficacy changes be filed at the time the change is implemented.

2.1.4 Level IV - record of changes

Level IV or Record of Changes (Quality only) are changes to a new drug that are not Level I, Level II or Level III and are not expected to impact the safety, efficacy, quality and/or effective use of the drug. The changes included in this reporting category may be implemented by the sponsor without prior review by Health Canada. The changes should be retained as part of the drug product's record by either the sponsor or the manufacturer and comply with Good Manufacturing Practices (GMP) requirements of Division 2 of the Food and Drug Regulations.

2.2 Drug submission filing information

2.2.1 Related guidances for drug submission filings

The following Health Canada guidance documents provide instruction regarding submission filing, procedures and review target dates and should be consulted by the sponsor when preparing a drug submission. For the convenience of the reader, some of the detail included in these guidances has been included in the following sections along with additional detail regarding post-NOC change submissions and Annual Notifications. These guidances are available on the Health Canada website.

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[3] Section C.01.014.5 of the Food and Drug Regulations states:
"Every manufacturer of a drug shall, annually before the first day of October and in a form authorized by the Director, furnish the Director with a notification signed by the manufacturer or by a person authorized to sign on his behalf, confirming that all the information previously supplied by the manufacturer with respect to that drug is correct".

Drugs for Human Use:
Guidance Document: Management of Drug Submissions

Drugs for Veterinary Use:
Guidance for Industry: Management of Regulatory Submissions

2.2.2 Pre-submission enquiries

The listings of changes in these guidance documents are not considered to be exhaustive such as to cover all possible situations. When in doubt as to the classification or supporting documentation, sponsors are encouraged to contact Health Canada in writing for clarification. Verbal enquiries should be followed-up in writing by the sponsor. Health Canada will provide a written response within fifteen (15) calendar days of a pre-submission enquiry.

To aid in planning the allocation of review resources, sponsors are encouraged to contact Health Canada regarding the number and proposed filing dates for planned changes to existing drugs. Sponsors should contact the appropriate directorate to determine the best method for submitting this information.

Refer to the Health Canada documents, Guidance Document: Management of Drug Submissions for drugs (drugs for human use) or the Guidance for Industry: Management of Regulatory Submissions (drugs for veterinary use) for contact information.

2.2.3 Submission filing - level I and level II changes

2.2.3.1 Drugs for human use

Refer to the Guidance Document: Management of Drug Submissions for details of where to send submissions for pharmaceuticals, biologics, and radiopharmaceuticals.

2.2.3.2 Drugs for veterinary use

Refer to the Guidance for Industry: Management of Regulatory Submissions for details of where to send submissions for pharmaceutical, radiopharmaceutical and certain biotechnological products[4].

2.2.3.3 Items to be included in the submission

The following items should be included, where applicable, in the submission package for all Level I and Level II post-NOC change submissions:

(a) A covering letter that includes:

- (i) the type of submission (i.e. SNDS, SANDS or NC)
- (ii) a narrative of the change(s) and a brief rationale for the change(s)
- (iii) any other information relevant to the submission
- (iv) an indication of the general type of supporting data (e.g., results of clinical, bioequivalence, toxicological or other in vivo studies including any in vivo/in vitro correlation studies [IVIVC]), supporting Quality [chemistry and manufacturing] data and the major Common Technical Document (CTD) sections included in the submission
- (v) for submissions filed in the electronic Common Technical Document (eCTD) format, include a description of the electronic submission including type and number of electronic media, approximate size of the submission, a statement that the submission is virus free with a description of the software used to check the files for viruses, and the regulatory and eCTD points of contact for the submission

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[4] The Veterinary Drugs Directorate (VDD) should be consulted to determine if the submission constitutes a veterinary biotechnological drug under the Food and Drugs Act.

(b) The completed documents to be included are:

(i) the Drug Submission Application Form (Health Canada 3011) signed and dated
(ii) the Drug Submission Fee Application Form
(iii) the Submission Certification Form - signed and dated

(c) Patent information pursuant to the Patented Medicines (Notice of Compliance) Regulations

(d) Good Manufacturing Practices (GMP) and Establishment Licensing (EL) Information

(e) Letters of Access for any supporting Drug Master Files and Site Reference Files

(f) An annotated and non-annotated electronic copy of:

(i) the Certified Product Information Document (CPID), and
(ii) the Product Monograph or Package Insert (for Veterinary drugs)

(g) Level I label changes for human drugs require bilingual Mock-Up Labels accompanied by the Packages Certification Form

(h) Level II Notifiable label changes for human drugs do not require Mock-Ups Labels. In place of Mock-Ups Labels, annotated written text is considered acceptable to reflect any proposed changes. Sponsors are expected to submit this written text in both official languages, as well as the Mock-Up Labels and the Packages Certification Form.

Data required to support the change(s) should be provided with the submission in electronic format as prescribed in the "Notice - Mandatory use of the Electronic Common Technical Document (eCTD) format" and the "Guidance Document: Preparation of Drug Regulatory Activities in the Electronic Common Technical Document Format" or the "Guidance Document: Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format" depending on the submission type. A Quality Overall Summary (QOS-CE or QOS-B) and a Comprehensive Summary: Bioequivalence (CS: BE) should also be completed and provided, where applicable.

For veterinary drug submissions, data should be prepared and filed as prescribed in the "Guidance for Industry: Preparation of Veterinary New Drug Submissions" and the "Guidance Document: Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format".

2.2.4 Level III - annual notifications

Level III changes submitted annually during the sponsor's Annual Drug Notification period should include:

(a) All Level III changes implemented for each new drug that has received a NOC and that have occurred in the preceding twelve (12) months; compiled using the Post-Notice of Compliance (NOC) Changes: Level III form[5]

Level III changes submitted at the time of implementation should include:

(b) a completed Post-Notice of Compliance (NOC) Changes: Level III form for each drug that has received a NOC

Note: a copy of the revised annotated labels, Product Monograph/Package Insert and/or CPID should only be submitted with the filing of the next Level I - Supplement or Level II NC that necessitates a label change or quality change as well. The dates of implementation for these Level III changes should be clearly identified.

Level III label changes do not require the submission of mock-ups under the Plain Language Labelling (PLL) requirements for human drugs. PLL does not pertain to veterinary drugs.

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5 Refer to the Notice - Post-Notice of Compliance (NOC) Changes: Notices of Change (

The supporting data for the Level III changes recommended in the associated guidance documents should have been generated prior to making the change but does not need to be submitted. However, the data should be available to Health Canada within thirty (30) calendar days if requested at any time.

Health Canada may periodically audit Level III changes by requesting and reviewing the supporting data from the sponsor as deemed appropriate. If the classification of the change or the data to support the change is not considered to be acceptable, the sponsor may be requested to file a Level I or Level II submission. In cases where the change has already been implemented, the sponsor may continue to sell the drug until such time as any issues are resolved. If Health Canada considers that the changed drug product has impacted the safety, efficacy, quality and/or effective use of the drug which may be harmful to the Canadian public, section C.01.013 of the Food and Drug Regulations will be applied.

2.2.5 Level IV- record of changes

The Quality changes included in this category should be retained as part of the product's record by either the sponsor or the manufacturer and comply with Good Manufacturing Practices (GMP) requirements of Division 2 of the Food and Drug Regulations. These changes should be annotated in the affected documents with the filing of the next submission to Health Canada.

2.3 Associated guidance documents

2.3.1 Post-Notice of Compliance (NOC) Changes: Safety and Efficacy

This guidance document contains detailed instructions with respect to the categorization of a change, specific change examples and the recommended supporting data for any changes to the Safety and Efficacy information including any labelling documentation, associated with the new drug.

2.3.2 Post-Notice of Compliance (NOC) Changes: Quality

This guidance document contains detailed instructions with respect to the categorization of a change and the recommended supporting data for any changes to the Quality information associated with the new drug including any labelling documentation affected by the change. Specific change examples are included in the appendices to this guidance.

Appendices

Appendix A: Acronyms

ANDS
Abbreviated New Drug Submission

BPS
Bureau of Pharmaceutical Sciences

BCANS
Bureau of Cardiology, Allergy and Neurological Sciences

BGIVD
Bureau of Gastroenterology, Infection and Viral Diseases

BMORS
Bureau of Metabolism, Oncology and Reproductive Sciences

CS:BE
Comprehensive Summary: Bioequivalence

CPID
Certified Product Information Document

CTD
Common Technical Document

DIN
Drug Identification Number

eCTD
electronic Common Technical Document

EL
Establishment Licence

GMP
Good Manufacturing Practices

ICH
International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IVIVC
In vivo/in vitro correlation

NC
Notifiable Change

NDS
New Drug Submission

NDED
Non-prescription Drugs Evaluation Division

NNHPD
Natural and Non-prescription Health Products Directorate

NOC
Notice of Compliance

NOL
No Objection Letter

OSIP
Office of Submissions and Intellectual Property

QOS
Quality Overall Summary

SANDS
Supplement to an Abbreviated New Drug Submission

SNDS
Supplement to a New Drug Submission

VDD
Veterinary Drugs Directorate

VICH
International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

YBPR
Yearly Biologic Product Report